ACUTE MYOCARDIAL INFARCTION IN MEN AND WOMEN - DIFFERENT IMPACT OF SMOKING IN THE TWO GENDERS

ANALYSES OF A COHORT STUDY OF 2281 PATIENTS ADMITTED TO HOSPITAL

BY

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ACKNOWLEDGEMENT

The present thesis is based on clinical studies performed at the Medical Department, Innlandet Hospital Trust Lillehammer during the years 1998 – 2010, and is funded by a research fellowship from the Innlandet Hospital Trust. This project has been a long journey involving 13 years of data collection. The work has been processed during the last three years in co-operation with the Department of Pharmacotherapeutics, Faculty Division Rikshospitalet, University of Oslo and the Institute of Health Management and Health Economics, University of Oslo.

I want to express my sincere gratitude to my main supervisor, Professor Åsmund Reikvam. Without his constant support and meticulous guidance, the doctoral program and production of the papers could not have been completed in about two years. He has been very generous in spending his time on this project. Being a cardiologist who has spent many years studying myocardial infarction, he has published many articles on the subject, and his expertise in this field and my discussions with him on about the results prior to publishing have been of great importance to my work.

I have been very fortunate to have had Professor Terje P. Hagen as a co-supervisor. His enthusiasm for sharing his knowledge of statistics in epidemiology, and his encouraging and positive attitude have been very valuable. We both had the thrill of learning new statistical procedures during this work, and I am very thankful for this.

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Finally, I want to thank Line, my wife and all the children in my family who have patiently endured my lectures on myocardial infarction.

What this thesis is about

It has been known for many years that smoking is a risk factor for myocardial infarction (MI). However, whether there are gender differences in the effects of smoking, implying that smoking is more harmful in women than in men has been debated but not settled. In the first half of the twentieth century men were hugely overrepresented among smokers in the Western world. As the occurrence of diseases caused by smoking became increasingly apparent, fewer men started smoking and more men gave up the habit, but this was not the case to the same extent in women. Altogether, smoking habits have changed substantially in Western civilizations during the last 20 years and this has also occurred in Norway, where smoking became about equally common in men and women from the early 1990s. Therefore we hoped that the present project with recently collected data could contribute to an improved understanding of the relationship between smoking and patients admitted to hospital with MI in the two genders.

The previous decade would be an appropriate period in which to collect clinical data that, could supplement the standard risk analysis of the smoking and gender issue based on population studies. Furthermore, the standardization of diagnosing and medical treatment of patients with MI represents a particularly suitable background for new investigations on this topic. Thus, the study explores information on patients diagnosed with MI in the hospital in Lillehammer. The data were entered consecutively into a database during the eight years from 1998 to 2005 and with further follow-up of mortality until September 2010.

It is the intention that this study will provide some of knowledge about MI in relation to smoking and gender. It is possible that this information may enable health workers and policy makers to evaluate whether there is a need for different policies and preventive measures in men and women.

LIST OF PUBLICATIONS

Study I

Grundtvig M, Hagen TP, German M, Reikvam A. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. Eur J Cardiovasc Prev Rehabil 2009;16:174-9.

Study II

Grundtvig M, Hagen TP, Amrud ES, Reikvam A. Mortality after Myocardial Infarction: impact of gender and smoking status. Eur J Epidemiol 2011;26:385-393.

Study III

Grundtvig M, Hagen TP, Amrud ES, Reikvam A. Reduced life expectancy after myocardial infarction - smoking is more harmful for women than men. Submitted september 2011.

ABBREVIATIONS

ECG	Electro cardiogram
HR	Hazard ratio
MI	Myocardial Infarction
NPR	Norwegian Patient Registry
TrI and TrT	Cardiac troponin I and T

1. INTRODUCTION

1.1 Epidemiology of myocardial infarction

After the Second World War there was a substantial increase in mortality from MI in Norway and it reached a peak level in the early 1970s, a level that changed little until the middle of the 1980s, when a steep decrease began, which has since continued in the 1990s and the 2000s[1, 2]. Data on the incidence of MI has been lacking in Norway due to the lack of relevant registries and databases. However, since the 1990s some information has been obtained from the Norwegian Patient Registry (NPR) – a national patient administrative register. The number of hospital admissions for MI decreased by 18% between 1991 and 2000. The decline noted in Norway in the period before 2000[3] was also found in other Scandinavian countries[4-6]. In the same period, varied results were reported in studies from the United States[7-12] and no firm conclusions could be drawn from that country[13].

The number of MIs reported to the NPR increased by 33% between 2000 and 2002[3, 14] – an increase that was mainly due to the new definitions of MI[15]. A proportion of patients who previously were diagnosed with unstable angina pectoris, now received the diagnosis MI. However, also after 2002 the number of MI admissions registered for MI in the NPR increased steadily and the NPR data in fact became increasingly unreliable. The increase was due to the fact that the NPR could not identify the patients on an individual level. A patient with MI after the introduction of coronary intervention as the preferred treatment for acute MI could be transferred between two or more hospitals for the same MI. Thus one MI could be counted two or more times. However, despite the increased number in the NPR, there are indications that the real incidence of MI observed in the 1990s continued the diminishing trend in the 2000s[1] (Figure 1).

On a population level in Norway, figures from the Cause of Death Registry (Statistics Norway) indicated a dramatic decline in mortality from MI, from a peak in 1987 to a much lower level in 2007 (from 189 to 79.7 deaths per 100,000)[1].

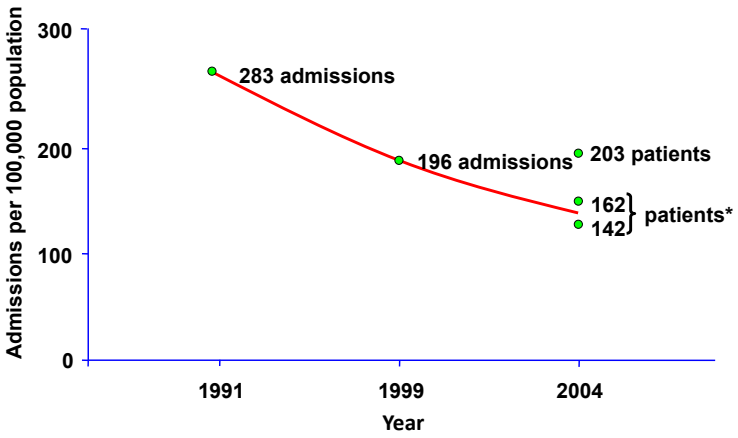


Figure 1. Trend in hospital admissions for acute myocardial infarction in Norway based on data from the NPR in 1991 and 1999 and estimated number of patients in 2004.
*adjusted and estimated for troponin diagnostics; the difference between patients and admissions is explained in the text.
Reproduced and adjusted with permission from Reikvam Å and Hagen T[1].

1.2 Risk factors for myocardial infarction

Smoking, elevated serum cholesterol and high blood pressure have for many years been recognized as the classic risk factors for coronary artery disease[16-31], but several other risk factors have been reported. The INTERHEART study[32] identified another six modifiable risk factors, namely diabetes mellitus, physical activity, abdominal obesity, psychosocial stress, high risk diet, and moderate alcohol consumption, although the latter did not turn out to be of definite significance. Dyslipidaemia and smoking were rated as the most important modifiable risk factors[32].

1.3 Gender and myocardial infarction

Numerous studies have shown that in general, women get MI later in life than men; an average delay of the order of 6-10 years has been reported[5, 33-36].

The mortality from MI in Norway has been changing rapidly in both genders since 1970 but with a more marked fall for men (Figure 2).

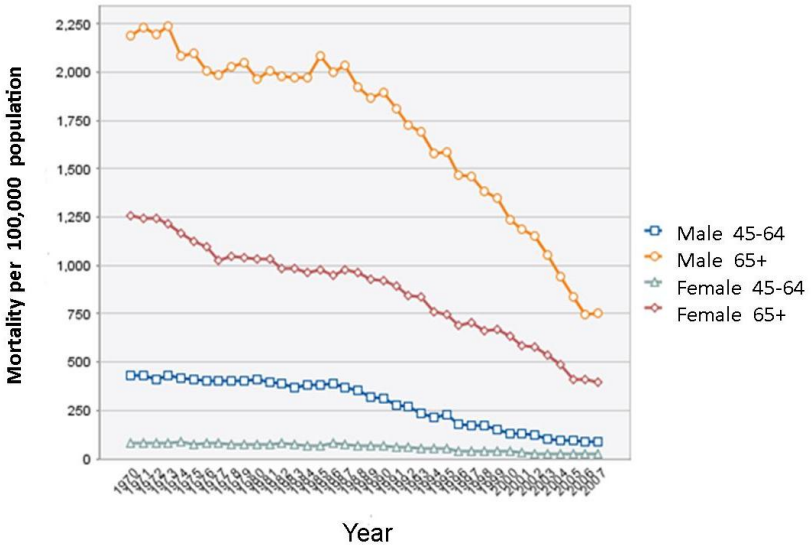


Figure 2. Mortality from myocardial infarction in men and women over a 37-year period.
Source: Folkehelseinstituttet.

As a consequence the proportion of deaths from MI for men relative to women declined considerably in Norway from 1998 to 2005, from 1.35 to 1.2 and further to 1.1 in 2009[37]. This means that the mortality from MI approached equality in the two genders.

1.4 Smoking and myocardial infarction

Smoking has an adverse effect on health[38-42] and reduces life expectancy[43-48]. Some studies have reported the equal importance of the risk factor of smoking in the two genders, whereas others have found some differences, mainly that smoking was more deleterious in women[49-61].

Smoking cessation programs have been shown to be strongly associated with increased smoking cessation rates[62, 63] and stopping smoking reduced the subsequent risk of MI[64-67]. Although the majority of patients try to stop smoking after an MI, one study found that about half were still smoking four years after the MI[68]. High smoking rates among women have caused an increased incidence of lung cancer and chronic obstructive pulmonary disease in the few past decades, and may also contribute to a less favourable MI incidence trend in the female than in the male population[69]. Increased smoking rates in women, together with diminished smoking rates in men, can explain the MI trends. There is no doubt that smoking is detrimental to health, and it is possible that there are gender differences with regard to adverse effects. However, more research on the gender issue is needed.

1.5 Epidemiology of smoking

Smoking habits have changed in Europe in recent decades, with a fall for men but a much smaller change for women[70]. In Norway, 20% of the population aged 16-74 years now smoke[71]. Smoking has

been about equally prevalent in both genders since the early 1990s. The data are based on 'Travel and holiday surveys' that has been collected on a random selection of inhabitants four times per year[71] (Figure 3).

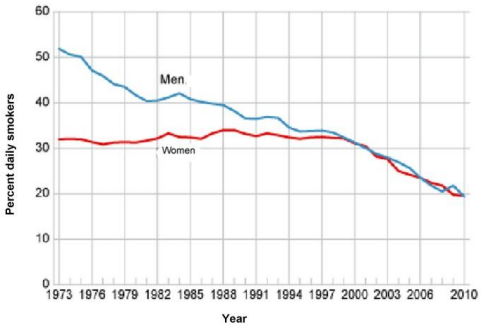


Figure 3. Percentage of daily smokers according to gender in persons aged 16–74 in Norway from 1973 to 2010.

With permission 2011 © Statistisk sentralbyrå[72].

The mean age of onset of smoking among ever-smokers was equal in the genders for the birth cohorts from 1947 but three and two years later in women than in men for the birth cohorts 1927-1936 and 1937-1946[73] (Figure 4).

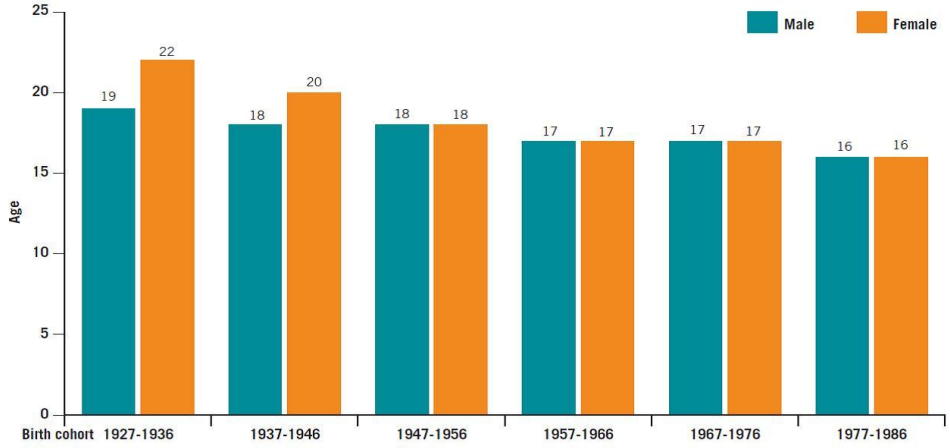


Figure 4. Mean age of onset of smoking among ever-smokers by gender and cohort. Pooled data 2004 – 2006.

With permission, 2012 Norwegian Institute for Alcohol and Drug Research (SIRUS)[73].

In some age groups more women than men now smoke in Norway (Figure 5). The data are based on the same surveys as for Figure 3[71].

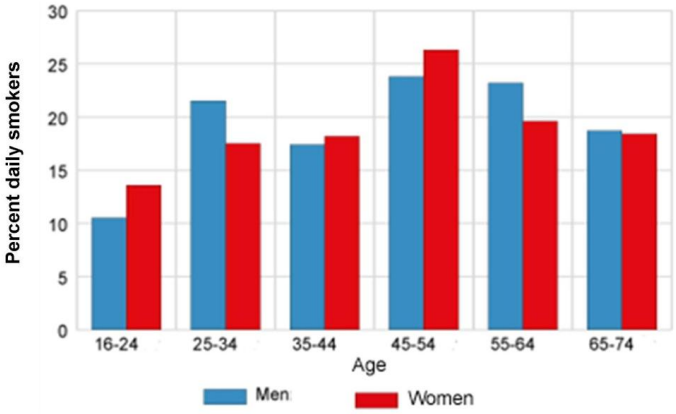


Figure 5. Percentage of daily smokers according to gender and age in 2010.
With permission, 2011 © Statistisk sentralbyrå[74]

In summary, over the past few decades the differences between the genders with regard to incidence of MI, mortality from MI, and smoking habits have changed. Against this background it seems probable that extensive data from the last decade on hospitalized patients – encompassing a smoking history – may be a valuable source of information for risk assessment in the two genders.

2. AIMS OF THE THESIS

2.1 General aims

The aim of this thesis was to assess the relationship between smoking and MI with a particular focus on possible gender differences in a cohort of hospitalized patients with MI.

2.2 Specific aims

- To quantify the extent to which smoking causes the first MI to occur prematurely in women and men.
- To explore mortality after MI with special emphasis on the impact of gender and smoking status and, furthermore, to investigate possible interactions between these variables during short- and long-term follow-up.
- To investigate whether and to what extent gender and smoking affect years of life lost/gained in patients with MI compared with age- and gender-matched life expectancy in the general population.

3. METHODS

3.1 Patient populations

Every patient with a permanent address in Norway who was discharged with acute MI, alive or dead, from Innlandet Hospital Trust Lillehammer, irrespective of age and ward of treatment, was included in the study. The study included patients from the years 1998 to 2005. Patients who died in the emergency department were included. Patients treated in the ambulance for MI as instructed by hospital physicians on the basis of communication with the ambulance personnel and electronically transmitted ECGs, were also enrolled in the study. Neither patients who were declared dead before admission to the emergency department nor patients with an MI first treated in another hospital were included. There were a total of 2733 acute MIs in 2281 patients.

There were no patients based on ambulance registration only. An MI was counted as a new event when the hospital had a first contact with the patient through admission to hospital or through the duty physician's contact with the ambulance service by pre-hospital transmission of ECG. Patients first admitted to another hospital (and not by the instruction to the ambulance service of the hospital's physician) were not counted. Care was undertaken to count an MI only once. Patients transferred between hospitals were only counted once for the same MI.

Study I

This first study included 1784 patients with a first MI, of whom 38% were women; mean ages of women and of men were 76.2±12.1 and 69.8±13.4 years, respectively. Among them, 26% had a history of angina pectoris. Significantly more women than men had diabetes mellitus, hypertension and history of angina pectoris. Women also had significantly higher serum cholesterol at admission. Current smokers and ex-smokers constituted 60.8% of the patients.

During work with the database over the next year it was found that 32 patients (1.2%) in the sample (2733) had been erroneously classified, either because they were foreigners, had had a previous MI, or the database entries were duplicates. The dataset (the first paper) was re-examined based on the adjusted sample but the results were similar and not significantly different from those first calculated.

Study II

Based on the index stay, 2281 patients were included of whom 1752 patients had suffered their first MI. Of these 2281 patients, 36.8% were women, and the mean ages for women and men were 76.0 and 70.2 years, respectively.

Study III

The patients were the same as in Study II, but the analyses were based on the last indexed MI for each patient, that is to say the MI last indexed in the inclusion period from 1998 to 2005. There were 738 patients with a previous MI. Of the female and male patients, 57.1% and 27.5% respectively had never smoked of the last indexed MI.

Years of life lost/gained were calculated as the age at death minus the life expectancy by gender groups for each county based on age similar to the patient's age at the last indexed MI.

3.2 Definitions of myocardial infarction

3.2.1 Definition used in the hospital between 1st January 1998 and 31st December 2000

MI was diagnosed according to World Health Organization criteria[75]. This definition is summarized in Norwegian in Hjerteforum[76].

Two out of three of the following criteria had to be present:

1. Retrosternal pain which may radiate to the neck, arms, or abdomen independent of respiration with a duration at least 20 minutes with no or transient effect of nitroglycerine. Accompanying symptoms may be nausea, vomiting, cold sweat, anxiety and dyspnoea or syncope/cardiac arrest.
2. ST segment elevation in one or more leads. Negative T wave development. After a few hours up to 1-3 days, development of Q waves with transmural infarction. New left (or right) bundle branch block, together with typical clinical signs.
3. Serum creatine kinase above 200 U/l for men and 150 U/l for women. Serum creatine kinase MB fraction higher than 10 µg/l.

For the diagnosis it was usually required to have a doubling or decrease to half of the initial creatine kinase value, depending on the timing of blood sampling, to get a positive result. The hospital analysed troponin I from the end of 1998 as described in the next paragraph, but the result was only used as a tool to exclude MI as a cause of the symptoms of the patient until 1st January 2001. With a normal troponin I level, MI was excluded.

3.2.2 The definition of myocardial infarction as stated by the European Society of Cardiology[15] was used in the hospital from 1st January 2001

Criteria for acute, evolving or recent MI

Either <u>one</u> of the following criteria satisfied the diagnosis for an acute, evolving or recent MI:

(I) Typical rise and gradual fall in cardiac troponin I (TrI). The following are biochemical indicators for detecting myocardial necrosis:

(1) Maximal concentration of TrI exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 h after the index clinical event, with at least one of the following:

(a) ischemic symptoms;

(b) development of pathologic Q waves on the ECG;

(c) ECG changes indicative of ischemia (ST segment elevation or depression)

(II) Pathologic findings of an acute MI.

Criteria for established MI

Any one of the following criteria satisfies the diagnosis for established MI:

(1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.

(2) Pathologic findings of a healed or healing MI.

With the introduction of the troponins many manufacturers produced various biochemical kits with different reference values. The kits for TrI had large variations and different reference values depending on the manufacturers of the kits, and there was no uniform definition of limits for the diagnosis of MI. It was even more difficult to get reliable reference values because for example “Dade Böhring” had three different platforms for the protein analysis: Stratus® CS - Dimension® - Opus®. The European Society of Cardiology/American College of Cardiology/American Heart Association had no recommendation for cardiac TrI assay performance versus standards for cardiac marker testing soon after the release of the new definitions. The guidelines stated that at least one value should be above the 99.0th percentile of normal which was 0.07 ng/ml for Stratus and Dimension. It was recommended that the imprecision should have less than 10% of the coefficient of variation at the risk stratification cut-off of the 99th percentile. The laboratory in Innlandet Hospital Trust Lillehammer used a kit from the end of 1998 from Abbot Laboratories AS with a cut-off value consistent with MI for TrI of 1.0 µg/l and a new kit from the same manufacturer from 22nd August 2002 with a cut-off value of 0.14 µg/l. The problem with the precision (coefficient of variation) for all troponin kits is visualized in Figure 6 for one kit used for analysing TrI.

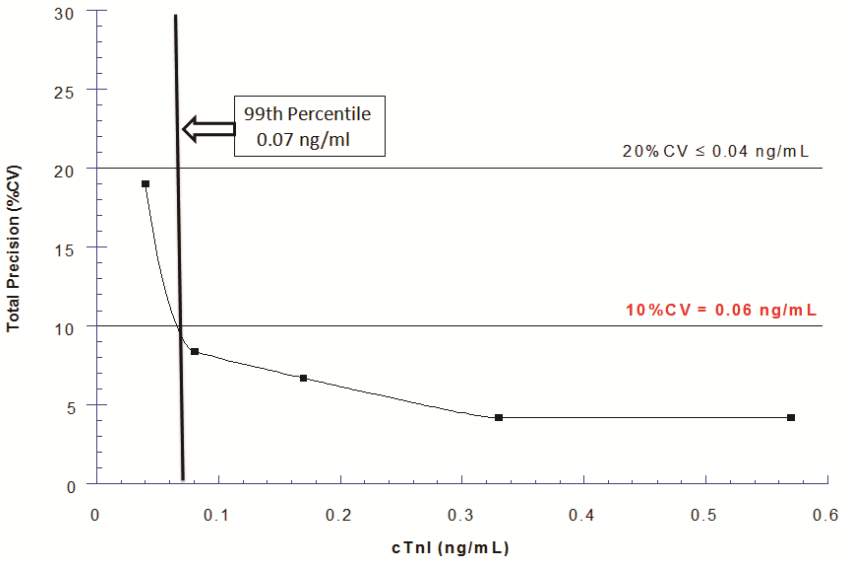


Figure 6. Low end precision of troponin I against total % precision (CV).
CV = coefficient of variation. Ng/ml=µg/l. cTnI=cardiac troponin I.

Very small infarcts can be found by use of more sensitive markers of myocardial necrosis, which are TrI and TrT, and thus infarcts of less than 1 g of tissue could be discovered. With the introduction of the troponins physicians were able to identify patients with a significantly increased risk of further adverse events and death[77-80]. The use of troponins for the definition of MI identified more definite MIs than the number obtained using the previous World Health Organization criteria. For example, 83% more infarcts in a Finnish study[81], 26% more in an unselected British cohort[82] and 58% more in an English hospital[83]. There were increased proportions of females with the new criteria for MI.

3.3 Choice of independent variables

The three factors of smoking, serum cholesterol and blood pressure were the classic factors for coronary artery disease at the start of the database[16-31].

It was also known that diabetes mellitus was an important risk factor[18, 84-88].

A high level of social support, and living alone were known to impact on the risk of outcome in MI[89-92]. Social status was therefore included.

Stroke had been shown to be an important predictor of in-hospital mortality[93] and peripheral vascular disease was a predictor of prognosis after MI discharge[94]. Since it was easy to obtain a history of stroke but more difficult to obtain information on peripheral vascular diseases, only the former variable was included.

The presence of heart failure had been shown to be an independent risk factor for death in myocardial infarction[95] as had necessary use of diuretics[96, 97]. Both the clinical parameter of heart failure and the use of diuretics in hospital and at discharge were therefore included.

Prescription of lipid modulating agents had been shown to be efficacious in primary and secondary prevention[98, 99], and with an effect also seen in elderly individuals[100-103].

Use of adrenergic beta-antagonists (beta blockers) has been established treatments during and after MI[104-109]. In-hospital use of both a fibrinolytic agent (streptokinase) and aspirin had been found to reduce the 30 day-mortality in a study with a 2x2 factorial design (ISIS2)[110]. For both drugs, the effects were independent and additive and this was a breakthrough in establishing the validity of using aspirin in MI.

The use of intravenous nitrate had been shown to reduce the mortality in a pooled analysis of six trials[111] and this drug was therefore included.

For in-hospital treatment and secondary prevention after MI, use of some beta-blockers[106, 109, 112-115] as well as use of angiotensin-converting enzyme inhibitors had been shown to improve survival, especially in patients with impaired myocardial function[84, 113, 116-118].

The use of digitalis during and after MI may be a marker of heart failure, but there was some uncertainty about whether it could reduce major cardiovascular outcomes[119-126]. The use of digitalis was therefore chosen as an independent variable.

3.4 Microsoft Access database

By the use of standard data collection forms, information on history, presenting features and treatment received was acquired.

The database was programmed in Microsoft Access 1997. Re-programming was undertaken by Morten Grundtvig because it was necessary to enter new parameters and new choices for existing parameters in newer versions. The database contained one administrative page and one MI page with automatic generation of unique MI IDs when new MIs were entered. The IDs were linked to date of birth and the personal 5-digit number. The database was accessible through most computers used by doctors in the medical department and by nurses in the cardiology section.

The registered parameters were the following: age; sex; family history; social status; working status; smoking status; history of treatment for hypertension; cholesterol value on admission; history of non-insulin and insulin-dependent diabetes mellitus; history of angina pectoris and previous myocardial infarction; history of stroke, deep venous thrombosis and pulmonary embolus; time from onset of symptoms to treatment; biochemical markers related to myocardial infarction; previous, in-hospital and discharge heart medications; treatment for heart failure in hospital; time of death. The information was written on case report forms (CRF) as soon as a patient was diagnosed with MI, and the CRF was kept with the patient's chart until discharge. The CRF was sent to the Coronary Care Unit where nurses typed the data into the registry. Dedicated nurses and Morten Grundtvig checked the database for missing values every month.

3.5 The patient administrative system DIPS

DIPS (Distribuert Informasjons og Pasientdatasystem i Sykehus) is the patient administrative system. It is based on modern technology: Microsoft Visual Studio, Oracle database and Borland Delphi programming and contains a number of components, including: Direct Oracle Access, from Allround Automations, Wptools, from Julian Ziersch Software, Quantum Express, from Developer

Express Inc., Reportbuilder, from Digital Metaphors Corporation and ImageLib Corporate Suite, from SkyLine Tools. The version used during follow-up was DIPS 4.2.2.2 Build 003. DIPS was available with complete electronic information from January 1, 1998 of patient records – except the handwritten temperature/drug charts, which were only available in paper format. The database allows listing of patients with specified diagnostic numbers from ICD 9 and 10 according to time intervals. The system was updated online every fourteen days, registering deaths and dates of death from the Norwegian Death Registry administered by Statistics Norway. Report D737 allows identification, within a specified period, of every deceased person who had been in contact with the hospital at any time. This file was merged with our database using the official 11-digit personal number to identify deaths of patients.

3.6 Statistics

For Study I statistical analyses were performed with SAS, version 9.1 (Cary, North Carolina, USA).

For study II statistical analyses were performed with Statistical Package for Social Sciences, PASW Statistics, version 18.0.2 (SPSS Inc. Chicago, Illinois) and verified by SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

For study III, statistical analyses were performed with IBM SPSS Statistics Version 19. The initial analyses for the structural equation modelling with Amos 19.0.0 (Build 1376) and the final analysis of this analysis was done using SAS version 9.2 (Proc Calis and Proc Reg; SAS Institute Inc., Cary, NC, USA).

Risk factors other than the variables describing age, time and cholesterol levels were coded as categorical variables, with reference units (no events) given the value of zero. The male gender and living alone were coded zero. Bivariate comparisons for categorical variables were made by Pearson's Chi-squared tests. Other variables were described by mean and standard deviation or mean and standard error, and comparisons between groups were made by Student t-tests within a general linear method (GLM) procedure.

In Study I the association between risk factors and age at the first MI was analysed by multivariate regression within a general linear model. Explicit tests of the gender differences in the effects of smoking on age at first MI after control for relevant confounders were performed within a model including interaction terms between genders and smoking status (i.e. gender × ex-smoker and gender × current smoker).

Study II used logistic regression by the forward Wald method for analysing the effects on mortality by possible confounders; smoking history and gender, including the interaction terms between genders and smoking status were entered at the last step.

For the analyses of the effects of smoking history and gender differences on death after discharge, Cox regression analysis by the forward Wald method was used, including possible confounding variables. The same interaction terms between sexes and smoking status were used.

In study III the actual age at death was subtracted from the projected age of death at the time of the MI – based on age- and gender-matched life expectancy in the general population – to yield year of life lost/gained. In bivariate analyses Student's t-tests were used to determine differences between the genders with regard to years of life lost.

Years of life lost/gained was used as a dependent variable in multivariate analyses using structural equation modelling to determine the relative importance of risk factors among the patients.

3.7 Formal requirements

The study has been approved by the Privacy Ombudsman for Research, Oslo University Hospital, division Ullevaal, Oslo. The investigation complies with the principles outlined in the Declaration of Helsinki.

4. SUMMARY OF RESULTS

4.1 Study 1. Investigation of how smoking affects age of onset of first MI in women and men

Unadjusted mean ages at first MI were 76.2 years for women and 69.8 years for men, a difference of 6.4 years (P < 0.001). Mean age within the various groups was: women non-smokers, 80.7 years, women smokers, 66.2 years – a difference of 14.4 years (P < 0.001); men non-smokers 72.2 years, men smokers, 63.9 years – a difference of 8.3 years (P < 0.001).

After adjustment for risk factors (hypertension, cholesterol levels, diabetes) and patient characteristics (history of angina, history of stroke) 13.7 years of the age difference in women were attributed to smoking; the corresponding figure in men was 6.2 years (P<0.001).

4.2 Study 2. The impact of smoking and gender on the mortality after MI

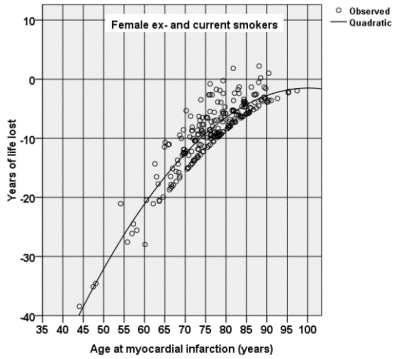
The mean age for women at admission was 5.8 years higher than for men (76.0 vs. 70.2 years) and women were less likely to have been smokers. In-hospital mortality for the first MI was 8.9% for men and 13.3% for women, and total mortality levels for all indexed MI after seven years were 47% for men and 61% for women. Using Cox regression analysis, with all indexed MIs included, the after-discharge mortality for women was significantly lower than for men (hazard ratio 0.82; 95% confidence interval 0.70–0.96; p = 0.015). Compared with non-smokers, patients who were smokers on admission had significantly increased seven-year mortality after discharge (hazard ratio 1.30; 95% confidence interval 1.03–1.63; p = 0.002).

A study of the cause of death was undertaken by randomly examining a selection[127] of 20% of the patients discharged alive (N=183) after the last indexed MI; 71.6% died from definite or highly probable cardiovascular disease, 18.6% of other causes, and 9.8% of unknown causes. Similarly, a 10% random sample of patients who died in-hospital during the index MI showed that only 1 of 34 patients died of other causes than cardiovascular disease. Therefore, an estimated 85% of all those who died (in-hospital and after discharge) of the total sample (N=1259) died from cardiovascular diseases and 15% from other causes.

4.3 Study 3. Investigation of how smoking affects years of life lost/gained after MI in women and men compared with age- and gender-matched groups in the general population

During follow-up, it was found that more than 55 % of the patients had died. Bivariate analyses showed that both female and male non-smokers lost 5.4 years of life, whereas smoking women and men lost 11.6 years and 9.7 years (p=0.07), respectively; corresponding figures for ex-smokers were 7.8 years and 6.0 years (p<0.001). In multivariate analyses, years of life lost were strongly related to age at the MI and significantly related to the quadratic term of age. Examples of years of life lost versus age at myocardial infarction are visualized in figure 7.

Panel A



Panel B

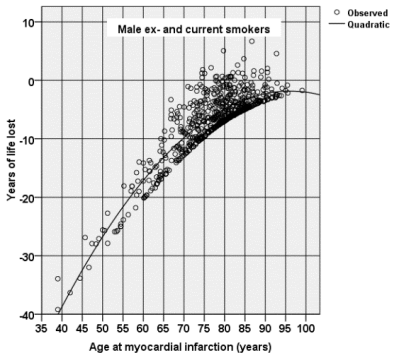


Figure 7. Years of life lost versus age at myocardial infarction for female ex-smokers and current smokers (panel A) and for male ex-smokers and current smokers (panel B).

By use of structural modelling equation it was found that figures for years of life lost were similar in non-smoking women and men. Smoking men lost 4.2 years more than non-smoking men. Female ex-smokers and current smokers lost 1.8 and 1.9 years more than the corresponding groups of men.

5. Methodological considerations

5.1 Patients

The patients examined were those with a permanent address within the hospital's catchment area, and people on holiday or business trips with permanent addresses in other parts of Norway. Patients who were admitted to other hospitals when staying outside the catchment area of Innlandet Hospital Trust Lillehammer, were not included. Exports and imports of patients have not been studied. Because Gudbrandsdalen is a popular valley to visit for holidays there may have been more imports of patients than exports. However, only 6.4% of the patients had a permanent address outside the ordinary catchment area of the hospital, indicating that the vast majority of the patients resided within the catchment area.

About 80% of the population using the hospital in Lillehammer for acute admission lived further away than 15 km. In this respect the hospital compares to other populations in Norway. However, more than 20% of the population had to travel further than 115 km, and a small proportion lived more than 200 km away from this hospital, implying very long transport distances. In fact, these distances are comparable to few other areas in Norway except the counties of Northern Norway.

Only slightly more people were daily smokers in the county Oppland (24 %) than in the whole country (22%) in the 5-year period 2005-2009, and smoking status was therefore representative of Norway as a whole[128]. Death rates from ischemic heart disease have been somewhat higher in Oppland than for the average in Norway; the death rates per 100,000 in 2003 for men were 201 vs. 179 for Norway as a whole, while the corresponding figures for women were 118 vs. 85[129]. This means that our study patients may have had more pronounced risk factors for ischemic heart disease than the average Norwegian population.

The study is only valid for patients with MI who reached hospital alive. Some individuals might suffer an MI without being transferred to hospital or may die before reaching hospital. The possibility that smoking, age or gender influence the chance of being admitted to hospital with MI could be considered.

Undoubtedly, patients with recognized MI without contact with hospital services constitute a minor proportion of the total number of patients with MI. It is possible that a few patients in nursing homes are treated on location, without admission to hospital, because they have other advanced diseases (e.g. advanced cancer or dementia). This situation would in any case apply to the oldest part of the MI population and would slightly influence the age of a first MI and years of life lost. The literature does not give any indication that men and women are differentially admitted to hospital according to patient or physician choices.

However, there are a fairly large number of patients with unrecognized MI during the event. In an evaluation of the Framingham data these accounted for 25% of the MIs, and almost half of those were "silent", with a higher incidence in patients with diabetes mellitus and in the elderly[130]. The proportion of all infarcts that were unrecognized was higher in women and in older men; 30% of the unrecognized MIs in men were <55 years of age and 60% of the unrecognized MIs in women were < 65 years of age. Therefore, if one tries to make calculations that include unrecognized MIs in a total MI equation, it

cannot be ruled out that age at first MI could differ somewhat from our results and that findings related to gender could also differ.

The proportion of patients with MI who dies out of hospital is substantial[131]. In a study from Sweden[132] it was estimated that three times as many individuals with supposed MI (sudden deaths included), including first and later MIs, died out of hospital compared to those who died in hospital, and that these patients constituted one third of the total MI population. The female gender has been associated with lower risk of out of hospital death[132, 133] (odds ratio 0.85, 95% confidence interval 0.83-0.87[132]). Persons aged 35 – 54 years constituted 17.4% of out of hospital deaths related to coronary heart disease. This means that the major proportion of out of hospital deaths occur in people of older age. On average they were two years younger than hospitalized patients who died within 28 days of the MI event[132]. It is unlikely that inclusion of the out of hospital MI deaths in our total MI material would significantly change the relative contribution of the genders with regard to the age at the first MI.

Another study reported that the number of individuals who died from MI outside hospital was four times higher than the number of MI deaths in hospital[134]. The studies referred to[132, 134] included sudden deaths in patients with established coronary artery disease and previous MI, and these deaths are very often caused by electrical events or other cardiovascular diseases and are not related to a new MI.

We are not aware of any studies showing differential hospital admission for smoking versus non-smoking individuals with MI.

Based on the above-mentioned considerations it cannot be ruled out that the inclusion of unrecognized MIs in the MI population might impact on the age of occurrence of the first MI and years of life lost, but if so, probably to a minor extent. Definite documentation of any impact can only be obtained through rather complicated prospective epidemiological studies. However, our study was undertaken to analyse patients admitted to hospital with MI.

5.2 Statistical considerations

5.2.1 The MI cohort

In this study we examined a well-defined cohort (male and female with a defined disease) with a defined exposure (MI). Certain characteristics thought to be the most important at the time of designing the database were recorded. Based on the presence and level of the known characteristics (risk factors), covariate data were used to adjust for effect estimate (age at the time of the MI, mortality and years of life lost). This covariate effect can also be applied to disease-based sampling (case-control studies) and to cross-classification of the source population[135]. In our study we did not have any case-controls as we were examining effects that would not apply to controls. The study had a cohort design including a high number of exposed cases with the potential to identify relatively small differences in effect estimates. It had the advantage that it was protected against bias because of its prospective design. The outcome was easy to measure (age at the time of the MI) and the effect estimate contained hard endpoints (mortality and years of life lost). One of the effect estimates had a long latency in many cases (death), and follow-up over many years required personal endurance from the investigator in order to obtain mortality statistics.

All the confounders chosen were potential risk factors for the disease studied (MI) and were associated with the exposure (MI) being examined. In studying MI and outcome as described, age was found to be the most important factor. The HR with respect to age had to be written with three decimal places because to obtain the actual hazard, the number had to be exponentially multiplied by itself according to the age in years. The other confounders were coded zero and one, which made it relevant to denote HR with only two decimal places for those variables. It is important to code gender as zero and one (and not 1 and 2); otherwise the interaction terms between smoking and gender would receive erroneous coding.

In the design of the database, it was important to make no restrictions with regard to patient inclusion in order to avoid bias. Therefore, patients who died in the emergency department from MI were included. However, for practical reasons, some known confounding variables were not included in the database. These were: the number of cigarettes smoked daily, the amount of tobacco used for pipe smoking, amount of exercise, and information about dietary habits. In general, it is difficult to obtain reliable information on these parameters, and furthermore, the time available in our coronary care unit and medical wards did not allow us to obtain these data.

To study the effect of gender and smoking on in-hospital mortality we included all the possible confounding variables in a multivariate analysis. The confounding variables regarding medications given in hospital could have introduced bias since a number of patients did not receive the medication, although medically indicated, as they died very early after admission and before the medication could be administered. Fifty-seven (2.5%) of the patients died on the day of admission and only 10.5% of those patients were given an intravenous beta blocker vs. 55.6% of those 99 patients discharged or transferred to invasive centres on the first day. The corresponding values for intravenous nitroglycerine were 15.8% vs. 57.6%, and for fibrinolytic therapy 31.6% vs. 60.6%. This made the HR for the medications more favourable than would appear in a randomized trial. One way to study this effect could be to conduct the analysis after excluding patients who died on the day of admission. However, such analyses were beyond the scope of this study.

5.2.2 The risk factor of smoking

The risk factor of smoking, in particular the length of the smoking periods in men and women, needs to be taken into consideration when the aim is to assess the patients` age at the first MI, which in fact was the aim in paper 1. The habit of smoking was taken up later by women than by men. A vast gender difference with regard to the proportions of smokers in the two genders existed in the 1970s (figure 2, paper 1), as was also the case in the preceding decades. For example, in the 1950s the proportion of male smokers in Norway was as high as 76-78% among men born 1915-1934[136]. Another peak occurred in women around 1970, with the highest proportion of women smokers (52%) observed in women born 1940-1949[136]. After the 1970s the gender gap decreased steadily and the proportions of smokers in the two genders became about the same in the 1990s[137]. In recent years the proportion of daily smokers in Norway has been below 20%, with little gender difference[74]. In summary, a first wave of increased smoking occurred in men, and a second wave followed in women some decades later. As a consequence of this development more men were first put at an increased risk of MI and later on the same occurred to women.

However, during all the decades referred to, the commencement of smoking followed a similar pattern in the two genders. Both men and women started to smoke as teenagers or young adults. Figure 4 shows this pattern, and it is evident that the average ages of smoking onset have remained about the same in a wide variety of birth cohorts[73]. Accordingly, most male and female smokers among our MI patients were likely to have had a long smoking history, that is to say an exposure to tobacco smoke in the range of four to six decades. Moreover, this means that the exposure times are comparable in the two genders; if anything, women started smoking at a slightly older age than men. These considerations of exposure times may indicate that smoking is more harmful in women, as the first MI occurred more prematurely in women smokers than in men smokers – an estimation based on comparisons with non-smoking MI patients in the two genders (paper 1). In fact, not taking into account the slightly later commencement of smoking in young women, compared to young men, could imply an underestimation – considered to be minor – of the deleterious effects in women.

However, during the periods when smoking was on the rise among women, theoretically another pattern of smoking uptake and dissemination could have taken place. Women could have started to smoke later in life than men, for example at an age between 40 and 60. Then the exposure patterns would be different in the two genders, and our regression analyses would have been flawed. However, these deliberations are only theoretical as the smoking patterns are known, and are described above.

In the assessment of the exposure dose of tobacco, others have reported that male smokers have always consumed more tobacco than female smokers in Norway[138] (Internet reference in English[139]). If so, an increased risk and a worse outcome in men could be expected, which in fact is contrary to what we found. However, another relevant factor to this discussion is body weight. Women`s lower weight might mean that they do not tolerate as much tobacco smoke as men. Furthermore, biological gender differences, the importance of which has not been recognized, might have an impact.

The main differences between our strictly clinical study and epidemiological population studies should be noted. In the latter studies the endpoints may differ from those we investigated. For example, one might be interested in examining the development with regard to the number of myocardial infarctions in the two genders in the society (population). Then the matter of differential exposure would be important. In a period when smoking among women is increasing, young women will contribute disproportionately to a “women smoker group” whereas a more balanced age composition will be found in a “men smoker group”. Consequently, under such circumstances analyses of the exposures and the contribution of smoking to the MI development in the two genders will become more complicated. Although such epidemiological studies by nature are quite different from the ones undertaken by us and presented in this thesis, we have encountered the view that the same type of bias as described for the epidemiological studies pertains to our study. However, we hope that our elaborations in this chapter will elucidate this matter and clear away fundamental misunderstandings.

Also, another question arises – is it possible to define a denominator smoking population in the society, in men and women, from which the smoking MI patients are “recruited”? Before embarking on this discussion we need to be aware that the MI patients were included during an eight-year period, from 1998 to 2005 and that all hospitalized MI patients from this period were enrolled. This means that

the background smoking population, if it could be defined, had a complex composition, not least when taking into account that the risk factor of smoking – believed to be one of the strongest factors – on average had exerted an effect for some decades.

During our evaluations of this problem the view was put forward that MI cases may be considered stochastic events taking place at any time during the observation period of eight years, and accordingly the average age of the MI cases among smokers will reflect the average age of the smokers in the population. Correspondingly, the average age of MI cases among non-smokers will reflect the average age of the non-smokers in the population. Then it was asked whether the average ages of such putative denominator smoking and non-smoking populations could be recorded, and whether it would be possible in this way to obtain information about the relationships between the ages of possible denominator populations and the ages of the different MI groups. However, we consider this hypothesis to be too simplistic. In our opinion, in addition to some element of stochastic processes, specific external influences are more important, in particular exposure to tobacco smoke over many years. Thus, to record ages of potential denominator populations appears to be very complicated. Moreover, it is obvious that the average ages of the smoking men and women populations in the society are much lower – several decades lower – than the ages of the MI groups in our study.

If we had examined the ages of men and women smoking populations at a certain time in the observation period (1998-2005) through a survey on smoking habits, we would have had to consider that smoking had already taken its toll, as some individuals in this period might have changed their smoking status after having suffered an MI, and more importantly, a proportion of the smokers would have died, many of them from cardiovascular diseases. In particular, this would pertain to older smokers who, besides the age disposition, also would have had smoking exposure for as long as 60-70 years. Those suffering these outcomes would be so numerous that there would be an impact on the age of a potential smoking denominator population. Hence, background smoking populations in men and women, as well as the average ages of such populations, would in practice be hard to define, and in our opinion impossible to identify.

With all the above-mentioned limitations the most sensible way to perform assessments of the age at the first MI is to use multivariate regression analyses, starting with the ages of the men and women MI patients, which in fact was what we did in the first analysis (article 1). A prerequisite for this approach is that the main factors imposing risks for MI were known in our study. We think we collected key information about this matter, which we could then use for the analyses. We are aware that the results of multivariate regression analyses should be interpreted with caution, among other reasons because some confounding factors might have remained unidentified. However, it was particularly reassuring that one of the risk factors considered to be very powerful in relation to MI - exposure to tobacco smoke - seemed to be well controlled for and comparable in the two genders. As described above, the smoking patterns were essentially similar in the two genders. Thus it is probable that the difference between the average age at the first MI in smoking women and non-smoking women was causally related to smoking, and the same will be true for smoking men versus non-smoking men. Moreover, this is a biologically plausible explanation.

The particularly early occurrence of MI in smoking women, 13.7 years earlier than in non-smoking women, compared to a corresponding difference of 6.2 years in men, suggests that smoking is more harmful in women than in men. Such gender differences are consistent with findings from studies of heart-disease registries[140, 141] and they are also consistent with population-based study results[23, 142].

Admittedly, it may be problematic to make inferences about risk or life expectancy based on mean age of cases in different exposure groups such as gender or smoking when the mean ages of individuals in these different exposure groups in the population may differ. And this is possible for male and female smokers and non-smokers in the general population given differing time trends in smoking by gender. The lack of information about the denominator subgroups is a limitation of our study.

The smoking history had three categories, 'non-smoker', 'ex-smoker' and 'current smoker'. These categories were all coded zero and one. However, the current smokers had also smoked in the past (ex-smoker), but they did not fulfil the criterion of 'ex-smoker', namely to have stopped at least three months previously. The code for 'current smoker' was not weighted to adjust for this issue. Some might think weighting to be relevant.

5.2.3 Multivariate regression analyses

Mortality after discharge was analysed by Cox regression analyses. This is a robust statistical procedure in this study since the exact date of the MIs and all deaths were known for all the patients during follow-up. A missing parameter for only one of the confounding variables for an individual patient would exclude that patient from analysis. Therefore, it is very important to have complete data for all the confounding variables, as we had in this study, in order not to lose power that might be needed to detect differences using this statistic.

In the regression analyses the forward Wald method was used as a first step and 'enter' (forced entry) was applied to all the variables significantly associated with mortality, adding gender and smoking history as a second step. Two parameters could not be analysed at the same time due to interactions between the two, namely diuretic use in hospital and the clinical judgment of heart failure. These two were closely interrelated and produced non-sensible results with respect to HR. Although in principle, all the known parameters should be tested, the investigator should not be precluded from applying common sense when using statistics. As a consequence, only the use of diuretics was applied.

In the investigation of years of life lost as the dependent variable, an initial step was to use ordinary multivariate analyses. It became apparent that years of life lost was strongly related to age at MI which is logical because the younger one dies, the greater the loss of time to live. Using curve fitting for graphic presentation with regard to years of life lost versus age at MI, the best fit was quadratic. The significant parameters were age at MI, age square, insulin dependent diabetes mellitus, non-insulin diabetes mellitus and smoking history by gender (females losing more). History of hypertension and stroke were not significant risk factors in this model. It was apparent that the various measured and unmeasured risk factors had a profound effect on years of life lost through age, since each factor had a direct effect on years of life lost and an indirect effect through age. The final effect could be a combination of these effects. The risk factors for age at admission were analysed in a separate multivariate analysis, and additional parameters that were significantly related to age at admission

were presence of angina pectoris (no previous MI) and previous MI. Creating models for elucidating these interactions was feasible by applying structural equation modelling (sometimes called path analysis), using Amos (Analysis of Moment Structures) in the IBM® SPSS® statistical package. Structural equation modelling is thought to be more accurate than standard multivariate statistics to confirm relationships between observed variables. An unusual constellation was the quadratic interaction term 'age square' which was significant in multivariate analyses in addition to age. It turned out that the handling of this quadratic term was not possible in Amos and the analysis was therefore made in the statistical package SAS. The final analysis was carried out using the ordinary least square method using SAS and verified by IBM® SPSS®. The final analysis consisted of two steps to get the sum of the direct and indirect effects on the years of life lost.

5.3 Ethical considerations

The database was established in 1998. It was introduced to be used as a quality control tool for the medical department in the treatment of patients with MI, but also as a research tool from which to publish. At that time it was thought that it would not be in the interest of the patient to ask the patient for 'informed consent' to register data on mortality in the database, with the intent later to use the data in publications. In a stressful situation like an MI, this would in our opinion be entirely wrong and probably increase stress, worry and fear of dying. In MI studies undertaken before 1998, it was generally accepted not to ask for written informed consent. For example, this was the procedure used by the renowned ISIS (International Study of Infarct Survival) group in the randomized trials conducted during the 1980s, studies which also included many Norwegian patients[143]. Also, we found it unethical to retrospectively acquire informed consent from each individual at the start of this PhD-program in 2009, as more than half of the patients were dead and it would be inappropriate to get consent from relatives. Among those still alive, many patients were very old and we considered it inappropriate to bring up this matter.

The database contains a large number of patients, which makes it impossible for readers to identify individuals. Moreover, the database contains standard information and no data of a controversial nature. The Norwegian Data Inspectorate (Datatilsynet) is responsible for managing the Personal Data Act of 2000. However, the Inspectorate had appointed the Privacy Ombudsman for Research, Oslo University Hospital, Division Ullevaal, Oslo, to be responsible for research at Innlandet Hospital Trust, and thus also exempted the hospital from reporting to the Data Inspectorate. This is according to the 'Regulation of Personal Information' (Personopplysningsforskriftens) § 7-12, with reference to the law on 'Health Registries' (Helseregisterlovens) § 36. Accordingly, the handling of data in this study complies with the requirements for the 'Regulation of Personal Information' as specified in the regulation § 7-27. The Privacy Ombudsman for Research, Oslo University Hospital, Division Ullevaal, Oslo, approved the study with a waiver to obtain informed consent from the patients.

6. DISCUSSION

6.1 Age at the time of a first MI

In this study, women without additional risk factors (smoking, diabetes mellitus, hypertension, stroke, angina pectoris and hypercholesterolemia) suffered MI 10 years later than men without the same risk factors[144]. A parallel to this observation is the finding that in patients with familial hypercholesterolemia, ischemic disease appeared nine years later in women than in men[145]. This could indicate that the risk factor of elevated serum cholesterol affects the genders differently, implying that some protection against ischemic diseases is present in these women. However, the female heavy smoking group in that study experienced onset of ischemic diseases at the same age as the corresponding male group[145]. These results are consistent with our finding of only a moderately higher age, 2.7 years, for the onset of the first MI in smoking women compared to smoking men. In another recent study the same offsetting of the age difference for the debut of the first MI was observed[146]. These findings are consistent with the fact that smoking is most harmful in women, and in particular evokes premature ischemic disease in the female gender, a finding that is in line with other studies[147, 148].

The data are also consistent with those of population-based studies, which have shown a higher risk of smoking in women than in men in Norway, Denmark and Japan[23, 149, 150]. However, in some population studies, in particular the older ones, the gender difference in the effect of smoking was not found[17, 151, 152]. A recent large scale meta-analysis demonstrated a 25% increased risk in coronary heart disease in female smokers as compared with male smokers[153].

The INTERHEART study showed that the odds ratios for the effect of the risk factor smoking was stronger in women than in men[32], and after adjusting for levels of risk factors, the gender difference in the probability of MI cases occurring before the age of 60 was reduced by more than 80%[154]. However, the median ages for the gender groups from western Europe in the INTERHEART study[32] were more than ten years lower than in our study of unselected patients, which makes it likely that a selection of patients with MI occurred in that study.

In summary, the narrowing of the age gap between the genders for onset of ischemic heart disease in smokers is a strong indication that women are more affected by smoking than men. Our finding that a first MI occurred more prematurely in female than in male smokers[144] was not unexpected, but the magnitude of the difference, implying that twice as many years were lost – that is years free of MI – by female as by male smokers, was greater than anticipated.

It should be kept in mind that some major risk factors – cigarette smoking, elevated levels of cholesterol, high blood pressure, and diabetes – are present in the vast majority of patients with MI[155]. The INTERHEART study[32] reported that more than 90% of all cases of MI worldwide were predicted by modifiable risk factors in both genders and at all ages. These factors were abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low consumption of fruit and vegetables, and lack of regular physical activity. Consumption of alcohol was not of definite significance. These findings suggest that approaches to prevention can be based on similar principles all over the world and thereby have the potential to prevent most premature cases of MI. However,

with regard to gender differences, premenopausal women seem to benefit from some protection, which is lost once menopause is reached[156].

6.2 In-hospital and short term mortality

Mortality from MI should be studied with special attention to the characteristics of the study population. In particular, it is important to determine whether the sample is selected or unselected. Only in the latter case might it be representative of the population in a well-defined geographic area. Within the context of current-era clinical trials of ST-elevation MI and non ST-elevation MI, 30-day mortality rates of less than 2%-4% have been reported for selected patient populations[157-159], whereas mortalities in the range of 10 to 12% has been found in less selected patient populations[160]. However, large observational studies on non-selected patients still report MI mortality rates of nearly 20%[161, 162]. The overall in-hospital mortality rates in our study on unselected patients were 14.3% for women and 10.3% for men[163], which compares favourably with other studies[134, 162].

The finding of higher in-hospital mortality in women in our study was confounded by risk factors, and hence gender was not found to be an independent determinant in multivariate analysis[163]. While some have reported a worse outcome for women than for men in the short term[164-171], one study found lower in-hospital mortality in women[172], but most others have found few differences between men and women after adjusting for age, despite differences in treatment[173-189]. Because the presence of angiographic coronary disease has been reported to be less[190], equal[191] and more[183] in women compared to men, the diversity and poorer outcomes reported in women[192, 193] are likely to be related to differently selected patient populations.

Gender differences exist with regard to presentation and treatment in MI. Thrombolytics were less used in women than in men in our study[163] as in other studies[170, 194], but it is known that women with MI present less often with ST-segment elevation[183, 195, 196].

Some researchers have found that smokers who received thrombolytics had a better hospital survival than non-smokers receiving this therapy, but this was mainly confounded by age[197, 198]. Although there are differences in short-term mortality in subgroups of patients with acute MI, there is good evidence that men and women have an equal outcome and, furthermore, this is independent of smoking status, as we have found in our study of unselected patients[163]. The smoker's paradox[199-201], the fact that patients with a positive smoking history have lower mortality than non-smokers, emerges because of a different risk profile. After adjustments for confounders, primarily age, the difference in in-hospital mortality between the smoking and non-smoking groups, was no longer present[202].

6.3 Long-term mortality and smoking

Although no difference in mortality in relation to smoking history has been reported[203], our finding of an enhanced risk of death for smokers of 30% is consistent with the findings by others[67, 204, 205] of a diminished mortality risk for non-smokers, compared with smokers, in the range of one third to one half. One study reported that men and women who continued to smoke after an MI had 2.2 and 2.4 times the age-adjusted mortality, respectively, of those who stopped smoking[206]. In a review paper quitters were found to have a reduced risk of death after an ischemic event of 36-38% compared with continuing smokers[207, 208]. A post-hoc analysis of 18,885 patients with coronary artery disease,

showed that the difference in absolute event rates between current and ex-smokers was 4.5%[209]. This is more than twice as large as the decrease in absolute event rates between high-dose and moderate-dose statin therapy found in the IDEAL (1.7%) trial[210] and TNT (2.2%) trial[209]. Our analyses are based on smoking status at the time of the indexed MI, and we did not have information on smoking habits for individual patients in the follow-up period. One study found that although most patients stopped smoking soon after an MI, and a quitting rate of 71% was recorded after three months, continued follow-up over four years showed that an increasing proportion of patients restarted smoking, with the result that less than half of the smokers remained ex-smokers[211]. This is consistent with our finding of relatively high smoking rates at the time of an MI among patients with a previous MI; 27% and 18.8% (men and women) [163], as compared to 38.7% and 22.5% in patients with their first MI.

6.4 Long term mortality and gender

Our one-year mortalities for patients discharged alive were 14.5% in men and 16.7% (data not shown in articles) in women which compares with 18% and 22% in a similar recent study of unselected patients from Sweden[212]. Our 3-year and 7-year mortalities were 32.3% and 47% for men and 41.7% and 61% in women. The 3-year mortalities are somewhat lower in our study than in the Swedish study[212] (40.7% for men and 49.0% for women) even though they did not include patients who died before reaching the intensive care unit. Their patients were, however, somewhat older, men 2.5 years and women 3.2 years – which could account for the mortality differences. One possible explanation for the age difference may be the fact that a significantly lower proportion of the Swedish patients were smokers, 22% for men and 16% for women, versus 36.1% and 21.9%, respectively, in our study.

With regard to gender differences after adjustment for confounders, most studies have reported similar mortalities for men and women after MI. In different investigations, the 10-month-[213], one-year-[189], three-year-[214],five-year-[215] and 10-year-[84, 203] mortalities were similar for men and women. Lower long-term mortality for women than for men has also been found[172, 216], but these studies were selected with 80% women, and were undertaken in patients with chest pain with more than 50% of the patients being below 65 years of age. Our results from an unselected cohort showed a moderately lower long term mortality for women[163], which is consistent with two recent reports[212, 217].

6.5 Years of life lost

We found that the major factor affecting years of life lost in patients with MI, compared with age- and gender-matched groups in the general population, was current smoking. Male current smokers lost 4.2 years more than male non-smokers. Almost all of this difference was an indirect effect, arising because the MI occurred prematurely, at an early age. Other important findings were that ex-smoking and current smoking women lost 1.8 and 1.9 years more than the corresponding categories of men. The effects have not been quantified in this way before, and show the particularly deleterious effect of smoking in women.

There is an abundance of publications on mortality after MI and on the influence of different risk factors on this outcome, but to our knowledge the issue of years of life lost has not been reported. Some population-based studies on the effect of smoking, not specific to MI, have been carried out. An Icelandic study reported that the reduction of median life expectancy was greatest in "heavy" cigarette

smoking,13 years for men and 10 years for women[57]. A similar prospective study by Doll et al[43] in British male doctors showed that, compared to those who had never smoked, total years of life lost by smokers was on average 10 years. In that study there were very few censored (not deceased at the time of analysis) persons as virtually all died during the 50-year follow-up. In the Icelandic study 47% of the men and 65% of the women were censored. This compares to 50% in men and 46% in women in our study. However, the designs of those studies were different from our study and they did not investigate the years of life lost for each individual patient.

6.6 Limitations

There is evidence that smokers have a worse prognosis after MI than non-smokers. We do not know the post-MI smoking status of the smokers in this cohort. As previously mentioned, our data indicate that only a moderate proportion of the smokers did quit after their MI[163]. This finding should be viewed in the light of the probability of a higher risk of a new MI for those who continued to smoke after their first MI compared to those who quit. This implies that the risk of death in the current smoker group after discharge might have been underestimated.

In our study, some variables were unknown, such as the amount of tobacco used and possible exposure to passive smoking. Passive smoking has been shown to be important in relation to the occurrence of MI[218].

For studies 2 and 3, it was impossible to predict future events in those still alive. Ideally, risk factors, deaths, and years of life lost should be reported when almost all the patients are dead as was done in the study of Doll et al[58]. However, our study had a relatively long follow-up, during which more than 50% of the patients died, which is substantially higher than in most other studies[173, 215, 217, 219, 220].

Some risk factors reported to be important in population-based studies[32] were not available. These are related to exercise, dietary habits, waist to hip ratio, and psychological stress, and are usually difficult to quantify. Serum cholesterol values obtained at admission for an MI are not very reliable because they will decline significantly within hours of the onset of the MI[221] and because a proportion of patients have been treated with lipid-lowering medications for an unregistered period before the MI. For example, in our study 6.8% of the men and 8.1% of the women (difference p=0.363) had received cholesterol-reducing agents prior to admission, and for patients with a first MI who also had angina pectoris, 25% of the men and 16% of the women (p=0.019) had been given such drugs (data not reported in the articles). In addition, patients with chronic renal failure have worse outcome in acute coronary syndromes[222], but parameters for renal function were not entered into our database.

6.7 Future perspectives

Men and women differ with regard to the presentation and responses to treatment of ischemic heart disease[223]. Also, as concerns susceptibility to the harmful effects of smoking, there seem to be gender differences. However, hormones obviously protect premenopausal women[156] which is why young females usually avoid getting MI. By contrast, women seem to be become more susceptible after menopause. Health planners should implement programs to prevent young people from starting smoking and to encourage them to quit, and in this context should focus on the particularly harmful effects in women.

Further studies to explore and understand biologically the gender differences are warranted.

Worldwide, more than five million people die each year because of tobacco smoke[224]. A major improvement in the prevention of MI has been achieved through legislation banning smoking in public areas. It has been estimated that this has caused a decline in MI occurrence in the order of 17%, and the improvement is still on the rise[218]. In Norway this legislation was introduced in 2004. It is promising that further restrictions on smoking, including legislation to protect children from exposure to tobacco smoke, are being debated. It is the expressed view of The Norwegian Medical Association that Norway should develop into a smoke-free society. Hopefully, in the future we will have an even more ambitious goal; the elimination of tobacco smoking all over the world.

7. CONCLUSIONS

The present studies found the following answers to the posed scientific questions:

1. To quantify the extent to which smoking causes first MI to occur prematurely in women and men hospitalized with MI.

Smoking caused first MI to occur significantly more prematurely in women than in men, implying that twice as many years were lost – that is years free of MI – by women smokers as by men smokers. Smoking incurs a strong additional risk in women.

2. To explore mortality after MI with special emphasis on the impact of gender and smoking status and, furthermore, investigate possible interactions between these variables during short- and long-term follow-up.

Current smoking at the time of the indexed MI was associated with increased mortality after seven years follow-up. The smoking effect was independent of gender. Female gender was associated with a moderately lower risk of death during the same follow-up period.

3. To investigate whether and to what extent gender and smoking affect years of life lost/gained in hospitalized patients with MI compared with age- and gender-matched life expectancy in the general population.

MI caused a substantial number of years of life lost, with a heavier loss in current smokers than in ex-smokers and non-smokers. The effect was predominantly an indirect one, related to the patients' age at the event. Smoking reduced life expectancy more in women than in men, indicating that smoking is most detrimental in the female gender.

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I

II

III

Reduced Life Expectancy After Myocardial Infarction - Smoking is More Harmful for Women Than Men

Grundtvig, Risk factors, gender and loss of life

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Background The aim was to investigate possible gender differences in the years of life lost after acute myocardial infarction (MI) and to explore how smoking affects life expectancy in the two genders.

Design Clinical data were consecutively entered into a database and were analysed using structural equation modeling.

Methods In the years 1998–2005, 2281 patients (36.8% women) who were discharged from or died in hospital following a diagnosis of MI were included. Survivors were followed for a mean of 8 years. The age of death for each patient was subtracted from the average projected age of death for individuals in the general population with a similar age to the patient at the time of their MI. The effects of gender, smoking, and other risk factors on the years of life lost were analysed.

Results During follow-up, 55 % of the patients died. Nonsmokers, exsmokers and current smokers lost 5.4, 6.4 and 10.3 years of life, respectively. Structural equation modeling showed that currently smoking men lost 4.2 more years more than did nonsmoking men ($P<0.001$), and this was mediated through more prematurely occurring MIs. Female current smokers lost 1.9 years more than male current smokers and female exsmokers lost 1.8 years more than male exsmokers (both $P<0.001$).

Conclusions MI caused a substantial number of years of life lost, with a heavier loss in current smokers than in exsmokers and nonsmokers. The effect was predominantly related to the patient's age at the event. Smoking reduced life expectancy more in women than in men, indicating that smoking is most detrimental for the female gender.

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Keywords: smoking, myocardial infarction, sex, mortality, risk factors

The general life expectancy is high in Norway; in 2003 it was 77 years for men and 82 years for women and it has risen further since then.[1] The expected remaining years of life are calculated by Statistics Norway for every attained year of age, and according to the gender and county of habitation.[2] Calculations for the period 2000–2005 showed that men and women at 40 years of age could expect to live to 76.6–79.7 and 81.8–84.0 years, respectively, depending on their county of habitation (recent update of the web-site shows the period 2006–2010).

Myocardial infarction is a serious event entailing risk of immediate death or death in the subsequent years. Smoking is a prominent risk factor for cardiovascular diseases that might reduce life expectancy.[3] Whether there are gender differences in the effect of smoking – implying that smoking increases the risk of ischemic heart disease relatively more in women than in men – has been debated, but not settled.[4,5] In an investigation based on data acquired in hospital, we found that the first myocardial infarction occurred more prematurely in smoking women than in smoking men, 13.7 years and 6.2 years prematurely, respectively.[6] We also observed that smoking was associated with a gender-independent enhanced mortality during a 7-year follow-up period after discharge, whereas female gender on its own was associated with a moderately lower risk of death.[7]

Because of complex statistical relationships between risk factors, and the patient's age at the time of a myocardial infarction, traditional regression analyses are not well suited for estimating the effects of smoking on years of life lost. This is because the patient's age at the myocardial infarction is an intermediate variable that lies in the causal pathway between smoking and years of life lost. Therefore, smoking might have both direct effects on years of life lost, and indirect effects by causing myocardial infarction to occur prematurely. Structural equation modeling is a statistical method that allows investigation of relationships by quantifying effects along these pathways. To our knowledge, no former studies have used this statistical method to assess these relationships. Accordingly, the aim of the study was to investigate years of life lost after myocardial infarction and to analyse the effect of smoking history and other risk factors in both genders.

Methods

The study included non-selected patients with a permanent address in Norway who were discharged alive or dead from any department in the central hospital of the city of Lillehammer, Norway, with a diagnosis of acute myocardial infarction in the 8-year period 1998–2005 as described.[7] For those individuals with multiple myocardial infarctions occurring during the

inclusion period, only the last event was included in the analyses. The diagnosis of myocardial infarction before and after January 1, 2001 was based on the old[8] and the new[9] definitions, respectively.

We calculated the years of life lost for each individual (i) as:

Years of life lost$_i$ = AD$_i$ – LE $_{a, g, c}$,

where AD is the individual age at death and LE is the life expectancy calculated at the time of myocardial infarction by age (a), gender (g) and county (c). To reduce problems of stochastic variation, LE was calculated on the basis of averages from the years 2001–2005. Date of death was registered consecutively for patients dying in hospital and mortality dates were obtained on-line at regular intervals from the Norwegian Death Register, administered by Statistics Norway, for those discharged alive. Each subject's date of birth was subtracted from the date of death to yield the age at death (AD$_i$). Data on LE were provided by Statistics Norway.[2] The number of years of life lost is a negative value (AD$_i$ <LE $_{a, g, c}$) and the number of years gained is a positive value (AD$_i$ >LE $_{a, g, c}$).

Smoking habits were registered at hospitalization. If a smoking history was missing, the patient or his or her family was contacted by telephone to obtain the data. As a consequence, smoking history was known for all patients. The variable defining smoking had three categories: 'current smoker' if the patient smoked or had done so up until 3 months previously; 'exsmoker' if the patient was a former smoker and had stopped more than 3 months previously; and 'nonsmoker' if the patient had never smoked.

Any history of hypertension, stroke or diabetes mellitus were self-reported during hospitalization and verified against relevant medical charts.

Risk factors were coded as categorical variables with reference units (no events) given the value of zero. Male gender was coded zero and female one. Bivariate comparisons for categorical variables were made using Pearson's Chi-squared test. Continuous variables are described by means and standard deviation. Years of life lost are described by means and standard error. Bivariate comparisons were carried out using Student's t-tests.

Years of life lost and age at myocardial infarction were used as endogenous variables in a multivariate analysis using structural equation modeling to calculate the direct and indirect effects of possible risk factors.[10] Covariates in addition to smoking habits were gender, diabetes mellitus with and without insulin treatment, hypertension, a history of stroke, previous myocardial infarction, or angina pectoris (with no previous myocardial infarction). Because of a decreasing effect of increasing age at the time of the myocardial infarction on the years of life lost found in initial analyses, the age at myocardial infarction was described using linear and quadratic terms. The quadratic term 'age at myocardial infarction squared' was included to capture the marginal decreasing effect of this variable. Additionally, we included interaction terms between gender and smoking status to capture possible differences in the effects of smoking between the two genders. In the final analysis of the direct effect of age at infarction, the estimate of years of life lost was calculated for the median age (75.3 years). These estimates are only valid for patients with an age of myocardial infarction between 40 and 100 years. The basic pathways to years of life lost are shown in Figure 1. Indirect effects in a pathway can be found by multiplying directs effects. The total effect of a factor on years of life lost is the sum of the direct, indirect and possible interaction effects. Insignificant effects in initial analyses were eliminated by a backward procedure and not included in the final model and the calculation of total effects.

Statistical analyses were performed using SAS version 9.2 (Proc Calis and Proc Reg; SAS Institute

Inc., Cary, NC, USA). Because our model was nonrecursive, ordinary least square and the more complex path model gave identical results and only results from the former are reported. All P values reported were from two-sided tests.

The study was approved on April 19, 2010 by the Norwegian Privacy Ombudsman for Research with a waiver for informed consent.

Results

The study consisted of 2281 individual patients (36.8% women) who were discharged alive or dead with a diagnosis of any last myocardial infarction during the years 1998–2005. There were 1543 patients with a first myocardial infarction (38.1% women). The ages of the patients at the myocardial infarction (men versus women) according to smoking categories were: nonsmokers 79.8±8.1 versus 82.8±7.2, P<0.001; exsmokers 74.4±10.3 versus 74.8±10.0 years, P=0.67; current smokers 72.7±11.1 versus 73.0±9.9, P=0.83. Characteristics and risk factors are given in Table 1.

During the follow-up – a mean of 8 years among the survivors – a total of 55.2% (N=1259) of the patients died, 50.1% of the men and 64.0% of the women (P<0.001). With increasing age, increasing proportions of patients above 60 years died in both genders. For patients aged less than 60 years, 11% of the men and 13% of the women died (difference P=0.70). Average ages at death were 79.8±9.0 for men and 82.7±8.5 years for women (difference –2.9 years: P<0.001). Cardiovascular diseases were the cause of ~85% of the deaths; an estimate based on examination of random samples of the patients, 20% of those discharged alive and 10% of those who died in hospital.

Compared with the general population, the years of life lost among patients with myocardial infarction were on average 6.8 years. Years of life lost were equally distributed between the genders in all risk categories examined using bivariate analysis, except for the groups exsmokers (P<0.001), current smokers (P=0.07) and patients with more than two risk factors (P=0.006), a group that showed a greater loss in women (Table 2). Exsmokers (N=426) had significantly more years of life lost than nonsmokers (N=555), 6.4 versus 5.4 years (P=0.001) and current smokers (N=278) a greater loss than exsmokers, 10.3 years versus 6.4 years (P<0.001).

The results from the structural equation analyses are reported in Table 3 and the direct, indirect and total effects of the exogenous variables are calculated in Table 4. In general, the indirect effects of the age at myocardial infarction on the years of life lost were stronger than the direct effects. This is most clearly illustrated for smoking men described by the variable ‘current smoker’, where the direct effect from current smoking on years of life lost was insignificant whereas the indirect effect through age at myocardial infarction was –4.20. Female smokers lost 1.94 years in addition to the 4.20 years lost by smoking men: altogether 6.14 years were lost compared with nonsmoking men.

Female nonsmokers (‘gender’) lost on average 1.63 years less than male nonsmokers through being older at the time of the myocardial infarction but lost 1.52 years more than men through a direct effect on loss of life with the result of having equal numbers of years of life lost as male nonsmokers. Thus, years of life lost after myocardial infarctions were similar for nonsmoking men and women.

Male exsmokers lost 0.41 years of life more than male nonsmokers. Female exsmokers lost an additional 1.84 years, altogether 2.25 years more than male nonsmokers.

Patients with insulin-dependent diabetes mellitus lost 1.75 years more than patients without this disease through their age at myocardial infarction, and an additional 0.69 years as a direct effect on loss of life. The risk factor 'non insulin-dependent diabetes mellitus' was only marginally related to altered loss of life in this analysis (0.5 years) compared with patients without the disease.

Discussion

In our sample of patients with a mean age of 72.5 years (men 70.4, women 76.2) at the myocardial infarction, bivariate analysis showed that nonsmoking patients experienced an average reduction of 5.4 years in their life expectancy. This is a substantial number of years lost, given that Norwegian men of 70 years of age have an average life expectancy of 12.8 years and women of 76 years of age can expect 11.2 years more.[2] Moreover, smokers had a particularly pronounced reduction of life expectancy, 10.3 years (both genders included) compared with the general population, indicating a strong harmful influence from smoking. It is also of note that exsmokers had slightly more years of life lost than did nonsmokers.

The structural equation model showed that the impact of smoking on years of life lost was not primarily a direct, but an indirect effect and came as a result of smoking causing the myocardial infarctions to occur prematurely. Furthermore, our findings support the notion that smoking, through this mechanism, is more deleterious in women than in men because female current smokers lost 1.9 years in addition to the 4.2 years lost by male current smokers; moreover exsmoking women lost 1.8 years more than exsmoking men. These results are in keeping with our previous finding of a more harmful effect of smoking in women by causing the first myocardial infarction to occur relatively more prematurely in women than in men.[6] The biological explanation for the gender differences might be that smoking women have a particularly enhanced risk of developing atherothrombosis in the coronary arteries, and this factor gives an accompanying increased risk of fatal cardiovascular events.

Besides smoking, patients with insulin-dependent diabetes mellitus turned out to have a significantly shorter life expectancy than patients without this disease; this finding is consistent with other reports.[11,12]

In general, smoking by itself and without any particular linkage to cardiovascular diseases is a strong risk factor for premature death. In a prospective population-based study, smoking was found to incur an average loss of 13 and 10 years – all causes of death included – in middle-aged men and women, respectively.[13] The British doctors' study on men recorded smoking habits in each decade over the age of 50 and found that those who continued to smoke died on average about 10 years younger than lifelong nonsmokers.[14] A 10-year loss of life for smoking men was also reported in the Whitehall study.[3]

Mortality from coronary disease has been declining in the Western world over the past decades, especially during the 1990s and 2000s, as shown in the USA,[15] Sweeden,[16] and Finland.[17] In all these studies and in the INTERHEART study,[18] smoking appeared as a prominent risk factor, which is consistent with our observations.

Interestingly, the smoking cessation rates in Norway have been higher for men than for women during the past decades and at present the smoking rate is about 20% in both genders, down from

52% in men and 30% in women in 1973.[19] During the same era the mortality from myocardial infarction in the population has been declining more in men,[20] so this more pronounced mortality reduction might be linked to a particularly marked decline in smoking in the male population.

A strong feature of our study was its unselected nature, as all patients hospitalized in the catchment area were included. It also contained extensive details about patient characteristics. Furthermore, we calculated the exact years of life lost/gained for each individual who died. This information enabled us to undertake multivariate analyses and provide information on how various factors contributed to years of life lost. We believe that our study is the first to undertake this kind of analysis.

A limitation of this study is that our analyses were based on smoking status at the time of the myocardial infarction, and we did not have information on smoking habits for individual patients in the follow-up period. We assumed that a certain proportion of current smokers abandoned smoking after the myocardial infarction, whereas it is unlikely that nonsmokers started smoking. However, our data indicate that only a moderate proportion of the smokers did in fact quit. This is inferred from the observation of high smoking rates at the time of the myocardial infarctions among those with a previous episode; in fact, in both genders these smoking rates were about two thirds of the rates of patients with their first myocardial infarction(data not shown).[7] In any case, it is likely that a proportion of those categorized as smokers in our analyses would have quit after the myocardial infarction, and this might have underestimated the harmful effect of smoking and the risk of death among smokers. Therefore, the estimation of years of life lost among those patients who continued to smoke until their death most likely would have resulted in even more lost years.

The patient's place of habitation was registered as their address of residence at the last episode of myocardial infarction; previous places of residence were not taken into account. Thus, some patients could have been given an incorrect life expectancy because this differs somewhat between counties in Norway. However, this was not likely to cause a major error as most of these patients were pensioners, who rarely change their place of habitation.

The calculation of years of life lost was based on an analysis of those who died (55.2%), with the proportion being highest in the oldest age groups. The actual years of life lost would increase if a high percentage of the younger patients still alive were to die within a few years. Conversely, if such patients would attain a near-normal expected lifespan, the overall years of life lost would not differ much from our estimates. However, there is no reliable method that can give predictions with regard to the lifespan of those still alive after the follow-up period.

In conclusion, life expectancy after myocardial infarction was generally reduced, more so in smokers than in nonsmokers, and with the largest reduction in women with a positive smoking history. Years of life lost were primarily the result of an indirect effect, caused by an onset of infarction at an early age.

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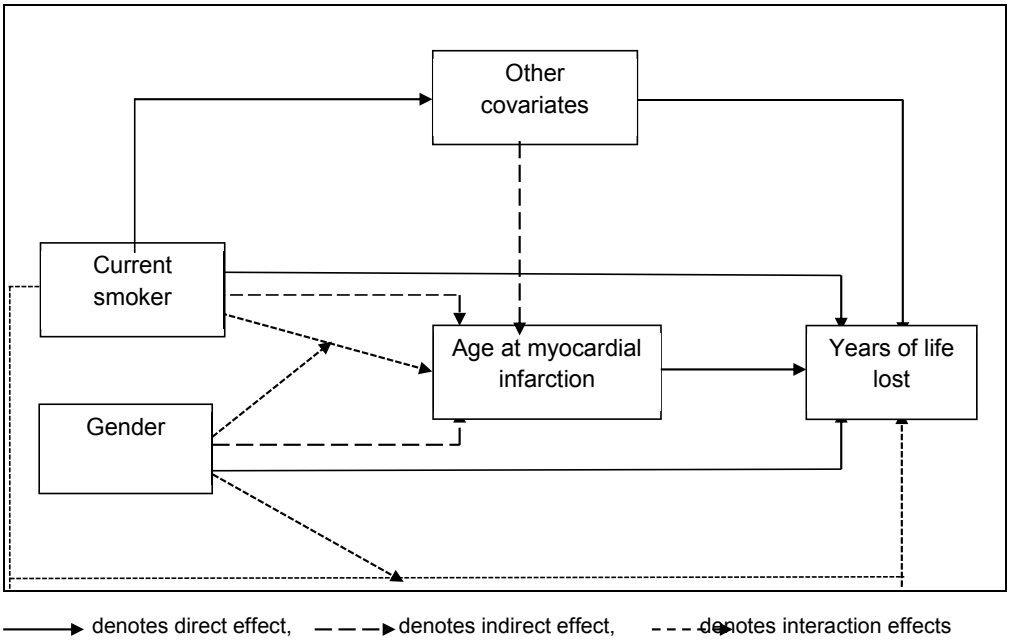

Fig. 1. Illustration of Direct, Indirect and Interaction Effects for Gender and Current Smokers.

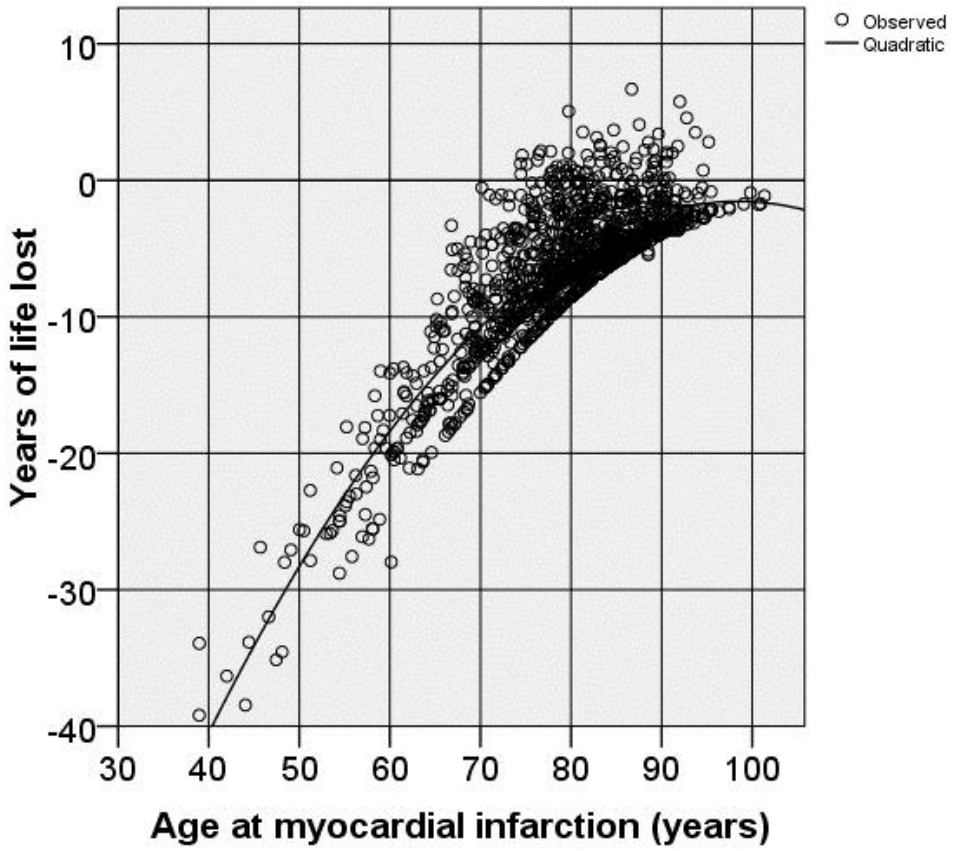

Fig. 2. Years of life lost versus the age at the last registered myocardial infarction in 1259 patients who died.

Table 1

Baseline characteristics for patients hospitalized with acute myocardial infarction in the 8-year period from 1998.[*]

Parameters	Total	Men	Women	Difference[§]	
					P value
Age (years±standard deviation)	72.5±12.6	70.4±12.7	76.2±11.5	–5.8	<0.001
Age squared (years^2±standard deviation)	5421±1738	5119±1719	5938±1646	–819	<0.001
	No. (%)	No. (%)	No. (%)	%	
Gender	2281 (100)	1442 (63.2)	839 (36.8)	26.4	<0.001
Nonsmoker	876 (38.4)	397 (27.5)	479 (57.1)	–29.6	<0.001
Exsmoker	728 (31.9)	544 (37.7)	184 (21.9)	15.8	<0.001
Current smoker	677 (29.7)	501 (34.7)	176 (21.0)	13.7	<0.001
Diabetes mellitus without insulin	224 (9.8)	128 (8.9)	96 (11.4)	–2.5	0.05
Diabetes mellitus with insulin	161 (7.1)	89 (6.2)	72 (8.6)	–2.4	0.03
Angina pectoris (no previous myocardial infarction)	383 (16.8)	208 (14.4)	175 (20.9)	–6.5	<0.001
Previous myocardial infarction	738 (32.4)	487 (33.8)	251 (29.9)	–1.4	0.06
Hypertension	832 (36.5)	457 (31.7)	375 (44.7)	–13.0	<0.001
History of stroke	316 (13.9)	197 (13.7)	119 (14.2)	–0.5	0.73

[*] If a patient experienced more than one myocardial infarction in the 8-year period, only the last myocardial infarction was entered in the analyses.

[§] Differences were calculated as values for men minus values for women and *p*-values were calculated using the Chi-squared test for categorical variables and by Student's *t*-test for age.

Table 2

Number of hospital patients with acute myocardial infarction

	Age groups (years)							
Gender	<40	40-<50	50-<60	60-<70	70-<80	80-<90	>90	Total
Male – no.	13	92	224	291	456	326	40	1442
% dead*	15.4	6.5	12.9	31.3	61.6	83.7	100	50.1
Female – no.	6	16	68	122	256	314	57	839
% dead*	0	18.8	13.2	36.9	67.2	80.6	96.5	64.0

*during mean 8 years of follow-up in survivors.

Table 3

Years of life lost among patients with a myocardial infarction in relation to life expectancy in the general population*

				Difference[§]	
Parameter	Total	Men	Women	Years	P value
Gender	–6.8 (0.2)	–6.8 (0.2)	–6.9 (0.3)	0.1	0.76
Nonsmoker	–5.4 (0.2)	–5.4 (0.3)	–5.5 (0.3)	0.1	0.89
Exsmoker	–6.4 (0.2)	–6.0 (0.3)	–7.8 (0.4)	1.9	<0.001
Current smoker	–10.3 (0.5)	–9.7 (0.6)	–11.6 (0.9)	1.8	0.07
Diabetes mellitus without insulin	–6.8 (0.4)	–6.4 (0.5)	–7.2 (0.6)	0.8	0.34
Diabetes mellitus with insulin	–8.4 (0.6)	–7.7 (0.8)	–9.2 (0.9)	1.6	0.17
Hypertension	–6.8 (0.3)	–7.1 (0.4)	–6.6 (0.3)	–0.6	0.25
History of stroke	–6.2 (0.3)	–6.1 (0.4)	–6.5 (0.4)	0.4	0.49
Risk factors[†]					
None	–5.1 (0.4)	–5.0 (0.6)	–5.1 (0.5)	0.1	0.93
One	–7.0 (0.3)	–7.1 (0.4)	–6.9 (0.4)	–0.2	0.75
Two	–7.2 (0.3)	–7.1 (0.4)	–7.4 (0.5)	0.3	0.63
More than two	–7.7 (0.5)	–6.9 (0.5)	–9.6 (0.9)	2.6	0.006

* Shown are risk factor analysis for 1259 patients (men n=722 and women n=537) who died among 2281 during a mean of 8 years of follow-up in survivors. Variables are listed as the mean and (standard error) in years.

[§] Differences were calculated as values for men minus values for women and P values were calculated using Student's *t*-test.

[†] Risk factors: current smoker, exsmoker, hypertension, any form of diabetes mellitus and history of stroke.

Table 4

Final analysis of the structural equation model of the estimate of years of life lost in relation to risk*

Variable	Age at myocardial infarction		Age at myocardial infarction squared		Years of life lost§	
	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
Intercept	78.35	<0.001	6,212.74	<0.001	–6.44†	<0.001
Age at myocardial infarction	—	—	—	—	2.28	<0.001
Age at myocardial infarction squared	—	—	—	—	–0.0116	<0.001
Gender	3.69	<0.001	585.82	<0.001	–1.53	<0.001
Exsmoker	—	—	—	<0.001	–0.41	0.02
Current smoker	–6.70	<0.001	–956.79	<0.001	—	—
Exsmoker × gender	–4.44	<0.001	–716.15	<0.001	—	—
Current smoker × gender	–3.20	0.008	–540.81	0.003	–0.90	0.008
Diabetes mellitus without insulin	—	—	—	—	–0.51	0.03
Diabetes mellitus with insulin	–3.60	<0.001	–558.76	<0.001	–0.69	0.01
Angina pectoris (no previous myocardial infarction)	2.24	<0.001	340.77	<0.001	—	—
Previous myocardial infarction	2.04	<0.001	295.95	<0.001	–0.52	0.001
Adjusted R square		0.18		0.18		0.78

* Shown are results for 1259 patients with a myocardial infarction who died among a total of 2281 during a mean 8 years follow-up in survivors.

§ The variables 'history of hypertension' and 'history of stroke' were not significantly associated with the years of life lost in the final analysis.

† This estimate was calculated for the median age at myocardial infarction.

Table 5

Years of Life Lost among Patients with a Myocardial Infarction through Direct and Indirect Effects*

Parameter	Direct effect	Indirect effect through age at myocardial infarction	Indirect effect through age at myocardial infarction square	Total effect years of life lost
Gender (male=0; female=1)	–1.53	8.42	–6.80	0.10
Ex-smoker	–0.41	0.00	0.00	–0.41
Current smoker	0.00	–15.29	11.09	–4.20
Exsmoker × gender	0.00	–10.14	8.30	–1.84
Current smoker × gender	–0.90	–7.31	6.27	–1.94
Diabetes mellitus without insulin	–0.51	0.00	0.00	–0.51
Diabetes mellitus with insulin	–0.69	–8.23	6.48	–2.44
Angina pectoris (no previous myocardial infarction)	0.00	5.12	–3.95	1.17
Previous myocardial infarction	–0.52	4.65	–3.43	0.70

* Shown are data in years calculated from Table 4. The total effect is the sum of direct and indirect effects.